Expectation and Dopamine Release: Mechanism of the Placebo Effect in Parkinson's Disease

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The power of placebos has long been recognized for improving numerous medical conditions such as Parkinson's disease (PD). Little is known, however, about the mechanism underlying the placebo effect. Using the ability of endogenous dopamine to compete for [^{11}C]raclopride binding as measured by positron emission tomography, we provide in vivo evidence for substantial release of endogenous dopamine in the striatum of PD patients in response to placebo. Our findings indicate that the placebo effect in PD is powerful and is mediated through activation of the damaged nigrostriatal dopamine system.

The simple act of receiving any treatment (active or not) may, in itself, be efficacious because of expectation of benefit (*1*). This is the placebo effect—a potential confounder in assessing the efficacy of any therapeutic intervention (*2, 3*). Placebo-controlled studies were designed precisely to control for such an effect (*4*). It has been assumed that the placebo response is not mediated directly through any physical or chemical effect of treatment (*5*). In Parkinson's disease (PD), the placebo effect can be prominent (*6, 7*).

We asked whether the placebo effect in PD is produced by activation of the pathway primarily damaged by degeneration [i.e., the nigrostriatal dopaminergic system (*8, 9*)]. To answer this question, we took advantage of the ability of positron emission tomography (PET) to estimate pharmacologically or behaviorally induced dopamine release based on the competition between endogenous dopamine and [^{11}C]raclopride (RAC) for binding to dopamine D_2/D_3 receptors (*10–14*). We hypothesized that if the placebo effect is mediated through the activation of the pathway relevant to the disorder under study, we should be able to detect placebo-induced release of endogenous dopamine in PD.

We examined the striatal RAC binding potential of six patients with PD (group 1, placebo group) under two conditions (*15*): Condition 1, a placebo-controlled, blinded study in which the patients did not know when they were receiving placebo or active drug (apomorphine) (*16*)—all patients received both placebo and active drug; and condition 2, an open study in the same patients without placebo.

We found a significant decrease in striatal RAC binding potential [17% for the caudate nucleus (range, 8 to 25%); 19% for the putamen (range, 8 to 28%); $P < 0.005$ for both, two-tailed paired t test] when the patients received placebo compared with open baseline observations (Table 1). This placebo-induced change in RAC binding potential was present in each patient and in each striatal subregion, although it was greatest in the posterolateral part of the putamen (Table 1). The magnitude of the placebo response was comparable to that of therapeutic doses of levodopa (*17*), or apomorphine (see below) (*18*). There were no differences in the striatal RAC binding potential between this group of patients when studied without placebo and a second group of patients matched by age and severity of parkinsonism studied exclusively in an open fashion (group 2, open group) (*15*) (Fig. 1).

These observations indicate that there is placebo-induced release of endogenous dopamine in the striatum (*19*). The estimated release of dopamine was greater in patients who perceived placebo benefit than in those who did not (*20*). This suggests a "dose-dependent" relation between the release of endogenous dopamine and the magnitude of the placebo effect.

We next asked whether there might be an interaction between the effects of the placebo and the active drug (*21*). The placebo response could synergistically enhance the benefit of an active drug, in which case double-blind, placebo-controlled studies would overestimate the active drug effect. Alternatively, the placebo effect could mask (or decrease) the specific effect of an active drug, which would lead to the opposite conclusion in the interpretation of a placebo-controlled study.

After adjusting for differences in "baseline" RAC binding potential, we found no significant differences in the response to apomorphine between the open group and the placebo group (combining patients who perceived a placebo effect and those who did not) (*22*). However, the degree of apomorphine-induced change in RAC binding potential tended to be lower in patients who perceived a placebo effect compared with those who did not and with patients studied in an open fashion (Fig. 2). We explored whether this observation could reflect a floor effect in the placebo group (i.e., whether the technique was insensitive for further reductions in RAC binding), but this did not appear to be the case (Fig. 3) (*23*). We conclude that the placebo response does not potentiate the effect of an active drug. Indeed, our results suggest that in some patients, most of the benefit obtained from an active drug might derive from a placebo effect.

The dopaminergic system is involved in the regulation of several cognitive, behavioral, and sensorimotor functions, and particularly in reward mechanisms (*24–28*). However, our experiments did not involve a direct reward. We conclude that dopamine release in the nigrostriatal system is linked to expectation of a reward—in this case, the anticipation of therapeutic benefit (*29, 30*). All patients were familiar with the effect of an active drug (levodopa), and such previous experience may have enhanced their expectation. We found that the level of expectation may determine experience (*20*)—patients who perceived a placebo effect had higher release of dopamine than those who did not.

Our observations indicate that the placebo effect in PD is mediated by an increase in the

Table 1. Striatal RAC binding potential (mean ± SD) of PD patients (group 1) scanned at open baseline and after receiving placebo ($n = 6$).

Site	Open baseline	Placebo	Mean percent change (range)
Head of caudate	1.964 ± 0.221	1.638 ± 0.230	16.6 (8.4–25.1)
Putamen			
Rostral	2.398 ± 0.342	1.976 ± 0.321	17.6 (5.3–26.3)
Intermediate	2.621 ± 0.438	2.142 ± 0.389	18.2 (7.4–27.0)
Caudal	2.095 ± 0.269	1.646 ± 0.261	21.2 (8.8–32.6)

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synaptic levels of dopamine in the striatum. Expectation-related dopamine release might be a common phenomenon in any medical condition susceptible to the placebo effect. PD patients receiving an active drug in the context of a placebo-controlled study benefit from the active drug being tested as well as from the placebo effect. By contrast, in the usual clinical practice setting, active drugs may be devoid of placebo effect. We found no evidence to suggest that the placebo effect synergistically augments the action of active drugs (in fact, a trend for the opposite was observed), so positive conclusions derived from placebo-controlled studies are not impugned by our findings.

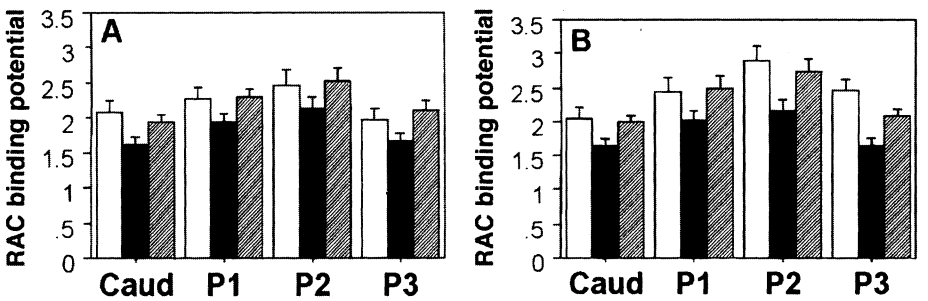

Fig. 1. Placebo-induced changes in RAC binding potential in the striatum ipsilateral (**A**) and contralateral (**B**) to the more affected body side of patients with PD. The ROIs are on the head of the caudate nucleus (Caud) and on the putamen, from rostral to caudal, P1, P2, P3 (*15*). Comparisons were made between the group of patients studied in an open fashion (group 2, open group; open bars) and the group of patients studied both with (solid bars) and without (hatched bars) placebo intervention (group 1, placebo group). Within-subject placebo-induced changes in RAC binding potential tended to be greater in the striatum contralateral to the more affected body side (20%) than in the ipsilateral striatum (17%). The placebo group and the open group did not differ in their baseline placebo-free RAC binding potential values [for the caudate nucleus, 1.96 ± 0.22 (SD) versus 2.07 ± 0.40, respectively; two-tailed t test, $t = -0.55$ (df = 10), $P = 0.59$; for the putamen, 2.37 ± 0.34 versus 2.42 ± 0.42, $t = -0.20$ (df = 10), $P = 0.84$]. Error bars, SEM.

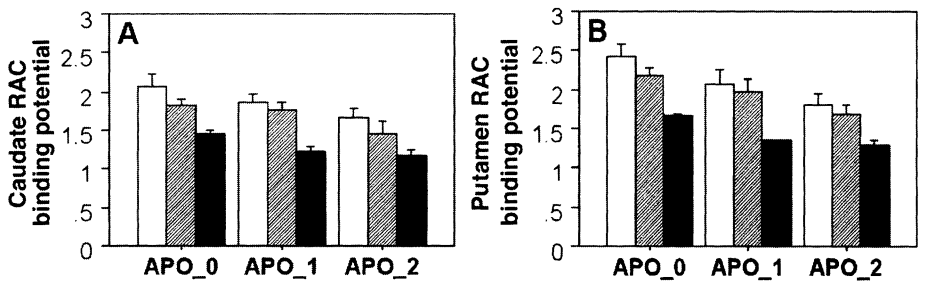

Fig. 2. Apomorphine-induced changes in RAC binding potential in the caudate nucleus (**A**) and putamen (**B**) before (APO_0) and after (APO_1 = 0.03 mg/kg, and APO_2 = 0.06 mg/kg) subcutaneous injection of apomorphine. Patients studied in an open fashion (open bars) had higher RAC binding potential values than those included in the placebo group [independently of whether they did not (hatched bars) or did (solid bars) perceive a placebo effect]. The decline in RAC binding potential induced by an incremental dose of apomorphine tended to be less pronounced in patients who perceived a placebo effect as compared with those who did not, and with patients studied in an open fashion: interaction term (group × apomorphine dose) evaluated by repeated measures ANCOVA, $F = 4.66$ (df = 2, 9), $P = 0.041$ for the caudate nucleus; $F = 3.40$ (df = 2, 9), $P = 0.079$ for the putamen. Error bars, SEM.

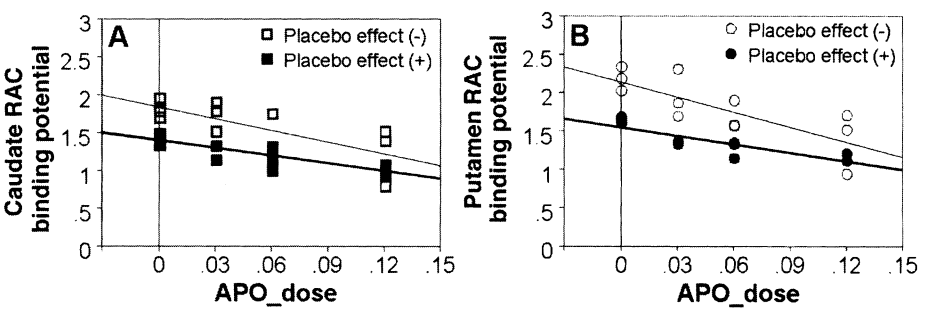

Fig. 3. Linear regression plots for patients without ($n = 3$; open symbols, thin lines) and with ($n = 3$; solid symbols, thick lines) perceived placebo effect: (**A**) caudate and (**B**) putamen RAC binding potential values against apomorphine dose (APO_dose). The four slopes were significantly different from zero ($P < 0.01$), but they did not differ significantly between patients with and without perceived placebo effect (for the caudate nucleus, –3.2 versus –5.1, respectively, $P = 0.28$; for the putamen, –3.8 versus –6.5, $P = 0.15$).

References and Notes

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15. All PET scans were performed in three-dimensional (3D) mode using an ECAT 953B/31 tomograph. We obtained 16 sequential frames over 60 minutes, starting at the time of injection of 5 mCi of [^{11}C]raclopride (mean ± SEM specific activity = 4692 ± 349 Ci/mmol at ligand injection). A time-integrated image with 31 planes, each 3.37 mm thick, was made from the emission data (from 30 to 60 minutes) for each subject. The five axial planes in which the striatum was best visualized were summed. On this time- and spatially summed image, one circular region of interest (ROI) of 61.2 mm^2 was positioned on the head of each caudate nucleus (Caud), and three circular ROIs of the same size were placed without overlap along the axis of each putamen (from rostral to caudal putamen: P1, P2, and P3); ROI position was adjusted to maximize the average radioactivity. The ROIs were replicated on the spatially summed image of each time frame. The background activity was averaged from a single elliptical ROI (2107 mm^2) drawn over the cerebellum on the summed image of two contiguous axial planes. The binding potential ($BP = f\,NS{\cdot}B_{max}/K_d$, where f NS is the free fraction of tracer) was determined using a tissue input graphical approach [J. Logan *et al.*, *J. Cereb. Blood Flow Metab.* **16**, 834 (1996)]. Further details of the PET scan protocol are reported elsewhere (*17*). We studied two groups of PD patients, of six patients each, under two different protocols as described below. Both groups were matched by age and severity of parkinsonism as measured by the Modified Columbia Scale (MCS) [R. C. Duvoisin, in *Monoamines noyaux gris centraux et syndrome de Parkinson*, J. de Ajuriaguerra, G. Gauthier, Eds. (Georg and Cie SA, Geneva, 1971), pp. 313–325]. Clinical details can be found on *Science* Online at www.sciencemag.org/cgi/content/full/293/5532/1164/DC1. After being pretreated with domperidone for 48 hours to prevent side effects, all patients underwent three consecutive RAC PET scans on the same day according to the following protocol: (i) either baseline or placebo scan 12 to 18 hours after withdrawal of medications; (ii) after subcutaneous injection of 0.03 mg of apomorphine per kilogram of body weight; and (iii) after subcutaneous injection of 0.06 mg/kg of apomorphine. The treatment order was maintained constant for all patients. Group 1 (the placebo group) was studied in a blind fashion—patients did not know when they were receiving placebo (subcutaneous injection of saline) or apomorphine (all patients received all three treatments). This group also received a fourth injection, consisting of 0.12 mg/kg of apomorphine on the same day, to explore the possibility of a floor effect

(see below). Group 2 (open group) was studied in an open fashion for comparison purposes (e.g., to investigate the effect of novelty on dopamine release). Here, recipients were scanned under all three conditions but knew explicitly if they were receiving no medication or which dose of apomorphine they were receiving at any given time. The advantages of this design are threefold: (i) It minimizes potential carry-over effects from the active drug (apomorphine) (*17*). (ii) It helps maintain the level of expectation throughout the study, which is crucial to this experiment. For example, the occurrence of apomorphine-induced side effects could "unblind" the study. (iii) It maximizes the tolerability of the procedure. In total, there was a 2.5-hour interval between scans (1-hour scan plus 1.5-hour break), sufficient to allow for decay of radioactivity, as well as for dopamine receptor recovery after apomorphine injection (*16, 17*). An additional open baseline scan was performed on group 1 patients on a different day to obtain placebo-free baseline values (interval between both sets of scans, 1 to 4 months). All patients had been contacted 1 month before the scans, and details of the protocol in which they were included were explained; they were reminded of these details 3 days before the scans. We avoided anticipation bias (e.g., patients' knowledge of the fact that the placebo effect can determine measurable changes in dopamine release might alter the results) by keeping the patients and the clinical staff unaware of the purpose of the study. In all cases, care was taken to optimize patient positioning in the scanner. Motion within and between scans was minimized by the use of a molded thermoplastic mask. All subjects gave written informed consent. The study was approved by the U.B.C. ethics committee.

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18. The placebo-induced change in striatal RAC binding potential is much higher than the reported within subject scan-rescan variation expected to occur within subject for scan and rescan (mean, 5%) [N. D. Volkow *et al.*, *J. Nucl. Med.* **34**, 609 (1993)]. The administration of 0.03 and 0.06 mg/kg of apomorphine led to a 14% and 26% decrease, respectively, in putamen RAC binding potential in the open group (see Fig. 2).
19. The increasing rostrocaudal gradient of the placebo effect (Table 1) eliminates the possibility that the results could be due to down-regulation of presynaptic D_2/D_3 receptors. Partial volume effects cannot explain the gradient in $BP_{open\ baseline} - BP_{placebo}$ reported here. Other considerations supporting our interpretation of the results can be found elsewhere (*17*).
20. Because the clinical benefit from apomorphine lasts typically about 1 hour (*16*), which is the duration of RAC PET scans, no objective measurements on changes in the clinical status after placebo or apomorphine injection were made (motor activity might confound the assessment of changes in striatal RAC binding potential). However, only half of the patients reported placebo-induced clinical improvement (comparable in magnitude to the clinical benefit obtained when they were on their regular treatment with levodopa). Although the number of subjects is small, those patients who perceived the placebo effect ($n = 3$) had higher changes in RAC binding potential than those who did not ($n = 3$) [for the caudate nucleus, 22% versus 12%; for the putamen, 24% versus 14%; $P < 0.05$ and $P < 0.01$, respectively, by analysis of covariance (ANCOVA)] (Fig. 2).
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22. Repeated measures ANCOVA gave the following results: For the caudate nucleus, between-group differences, $F = 0.03$ (df = 1, 9), $P = 0.87$; interaction term (group × apomorphine dose), $F = 0.09$ (df = 1, 10), $P = 0.77$. For the putamen, between-group differences, $F = 0.71$ (df = 1, 9), $P = 0.42$; interaction term, $F = 1.81$ (df = 1, 10), $P = 0.21$. The power for the interaction terms may not have been sufficient.
23. An apomorphine dose of 0.12 mg/kg led to a further decrease in RAC binding potential in the placebo group (Fig. 3). The total reduction in RAC binding potential (compared with placebo-free baseline values) was 42% in the caudate nucleus (range, 19 to 59%) and 46% in the putamen (range, 24 to 60%).
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